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Influence of Disease Severity on Fatigue in Patients with Parkinson's Disease Is Mainly Mediated by Symptoms of Depression

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Key Words
Parkinson's disease · Fatigue · Depression · Disease severity

Abstract
Purpose: Fatigue is a frequent non-motor complaint of patients with Parkinson's disease (PD). Despite increasing knowledge on fatigue, the factors leading to its development are still not recognised. The aim of this investigation was to test, using structural equation modelling, the hypothesis that the influence of disease severity on fatigue is mediated by symptoms of depression in patients with PD. ***Method:*** The sample consisted of 190 PD patients (93 men, 48.9%, mean age 68.2 ± 9.3 years, mean disease duration 6.4 ± 4.7 years) recruited from hospitals and outpatient clinics in the East Slovakia region. The Multidimensional Fatigue Inventory, the Hospital Anxiety and Depression Scale and the Unified Parkinson's Disease Rating Scale were used. LISREL was used to analyse the data. ***Results:*** Disease severity was directly associated with symptoms of depression (β = 0.26) and directly affected fatigue in terms of increased levels of general fatigue (β = 0.35), physical fatigue (β = 0.22), reduced activity (β = 0.31) and mental fatigue (β = 0.29), but did not directly influence reduced motivation. Symptoms of depression mediated the impact of disease severity on general fatigue (β = 0.25), on reduced activity (β = 0.31) and on mental fatigue (β = 0.28), but not on physical fatigue. Reduced motivation was not mediated, but directly influenced by more symptoms of depression (β = 0.82). ***Discussion:*** Since increased symptoms of depression mediate the impact of disease severity on three domains of fatigue in PD patients, disease management should focus on the treatment of PD and symptoms of depression.

Introduction

Fatigue has become a clinically important factor in explaining quality of life (QoL) in patients suffering from Parkinson's disease (PD) [1, 2]. Fatigue has been commonly reported in PD, affecting as many as 37–56% [3] or even to two-thirds of PD patients [1, 4], although physical and mental fatigue were also prevalent in the healthy population [5]. Those PD patients who suffer from fatigue perceive it as a symptom with a very high impact on

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their daily functioning [4] or QoL [2]. Mood disorders such as anxiety and depression are associated with poor health-related quality of life (HRQoL) in PD [6].

Cross-sectional prevalence estimates for anxiety and depression in PD have shown proportions ranging from 30 to 50% for each disorder [7–9] whilst older epidemiologic studies on depression in PD have prevalence rates ranging from 2.7% to more than 90% [10, 11]. Furthermore, in the age group comparable to PD patients, the prevalence of symptoms of depression was estimated to be 13.5% in the general population, while the prevalence rates for anxiety disorders ranged between 1.2 and 14% [12]. One French study [13] of prevalence rates of anxiety and depression in PD patients and in patients with other disorders showed that patients with higher symptoms of anxiety (Hospital Anxiety and Depression Scale (HADS)-Anxiety >8 symptoms) were more prevalent in PD (51 vs. 29%) than patients with higher symptoms of depression (HADS-Depression >8 symptoms) (40 vs. 10%). The difference between the proportions of PD patients and non-PD patients with enhanced symptoms of anxiety (22.4%) may vary between 12.2 and 32.5% (95% CI) in the population, whereas the difference in the proportions of those with depression (29.8%) was estimated to vary between 22.2 and 37.4%.

Symptoms of depression and fatigue are simultaneously associated with many illnesses, but in particular with cancer [14, 15], chronic heart failure [16], multiple sclerosis [17–21] and PD [22–24]. Increased symptoms of depression have a great impact on the course of PD in terms of functional status, activities of daily life and HRQoL [6]. In the last decade the relationships between fatigue, disease severity and depression have been investigated in PD patients and have shown strong correlations. Hagell and Brundin [3] found that depression and anxiety were the main predictors of fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue scale, FACIT-F) and that fatigue was associated with a lack of motivation, disease severity (Unified Parkinson's Disease Rating Scale (UPDRS)) and pain; however, they concluded that the role of anxiety was in contrast to what has been previously documented. Friedman and Friedman [25] showed in a 9-year follow-up study that fatigue was not correlated with disease severity or duration but with depression. Several studies reported that both symptoms of depression and fatigue are associated with a poor QoL [26]. In a study by Lou et al. [27], symptoms of depression were associated with all domains of fatigue as assessed using the MFI-20, except physical fatigue, and disease severity did not correlate with any of the domains of fatigue.

However, there is some overlap between fatigue and mood disorders, as fatigue is one of the DSM-IV criteria for both depression and anxiety. A recent paper by Skorvanek et al. [28] addressed the issue of primary fatigue, i.e. fatigue in the absence of depression, anxiety and excessive daily somnolence (EDS), and secondary fatigue, i.e. fatigue in the presence of depression or anxiety or EDS. In their study they found that both types of fatigue can be clearly distinguished and that they are associated with different clinical determinants.

As the associations between disease severity, depression and fatigue in patients with PD were predominantly based on bi- and multivariable analyses, we now report findings of path analyses conducted to explore the relationships between disease severity and symptoms of depression as factors that are generally considered as precursors of developing symptoms of fatigue in patients with PD.

Methods

Procedure

All eligible PD patients in the database records from outpatient neurologists and hospitals were asked for participation by means of a mailed questionnaire comprised of questions on sociodemographic background, medical history, current medication and self-report questionnaires among which were the HADS and the Multidimensional Fatigue Inventory (MFI-20).

Three weeks after receipt of the questionnaires and written informed consent, all patients were invited for an interview on relevant issues that were not part of the questionnaires and were checked for inclusion and exclusion criteria. After this structured interview, a neurologist assessed the disease severity of each patient using UPDRS Version 3.0 [29], including Hoehn & Yahr (H&Y) staging [30] and the Schwab and England Disability Scale [31]. All of the examined patients were in the ON stage during the interview and neurological examination. Patients who were not able to fill in the questionnaires due to impairment of their vision or motor impairment of their hands answered the questions during an oral interview. Caregivers were not allowed to provide questionnaires inputs.

Patients

This cross-sectional study evaluated symptoms of anxiety and depression, disease severity and fatigue in a study population of 190 patients with PD. The patients were recruited from one hospital (17 patients) and 18 neurology outpatient clinics (173 patients) in the East Slovakia region between February 2004 and November 2007. All patients were diagnosed in accordance with the UK PD Society Brain Bank Clinical Criteria [32] and their mental abilities were assessed with the Mini-Mental State Examination (MMSE) [33]. Exclusion criteria were as follows: (i) MMSE <24, as well as a negative response to an acute L-dopa challenge; (ii) secondary parkinsonism; (iii) sign of brain ischemia revealed by computer tomography; (iv) patients with pathological thyroid hormone levels,

and (v) severe comorbidity associated with the study variables – severe diseases where we expected patients not to survive for at least 4 years, or which could confound the main variables in our study, such as QoL and fatigue (e.g. rheumatoid diseases, end-stage renal diseases and others). The study was approved by the local Ethics Committee. Informed consent was obtained from each patient prior to the study.

Measures

Sociodemographic and Clinical Characteristics: Sociodemographic and clinical characteristics included age, gender, marital status, medical history and current medication, all of which were retrieved from patient records.

Fatigue

MFI-20: Fatigue was assessed using the MFI-20 as the primary outcome measure. The MFI is a widely used 20-item self-report instrument with good psychometric properties. It measures five domains of fatigue: general fatigue (referring to the general functioning of the subject, with statements such as 'I feel tired'), physical fatigue (somatic sensations directly referring to tiredness, for instance, 'Physically I feel only able to do a little'), mental fatigue (referring to cognitive symptoms such as having difficulty in concentration, for instance, 'It takes a lot of effort to concentrate on things'), reduced motivation (reflecting the motivation to start any activity, such as 'I dread having to do things') and reduced activity (a potential consequence of subjective fatigue, such as 'I think I do very little in a day'). Each domain contains 4 items, and the score on each item ranges from 1 (no fatigue) to 5 (very fatigued). The score for each domain ranges from 4 (no fatigue) to 20 (highest possible fatigue). The time frame is the last few days. MFI scales have shown good psychometric properties across several chronic diseases and languages [34–36] and good internal consistency (Cronbach's α across scales ranging from 0.80 to 0.94). In the current study, Cronbach's α yielded 0.72–0.84, which were all above what is minimally acceptable given the scale length and the average inter-item correlation [37–41].

Anxiety and Depression

HADS: Depression was assessed using the HADS. This self-administered scale simultaneously assesses symptoms of anxiety (HADS-A) and of depression (HADS-D). It consists of 14 items (7 for the assessment of anxiety and 7 for depression). All items are answered on a 4-point Likert scale from 0 (no problem) to 3 (extreme problem) with a score range of 0–21. The HADS is a reliable questionnaire that performs well in screening for the separate dimensions of anxiety and depression [42] and has been validated in PD study populations [13, 43–45]. In the present study, Cronbach's α was 0.70 for anxiety and 0.79 for the depression subscales. A cut-off score >8 for both subscales was used to quantify patients with likely anxiety and depressive symptoms, as this cut-off yields an optimal balance between sensitivity and specificity [42].

Four psychological distress symptom groups were defined by employing the classification of Pedersen et al. [46] and Bartels et al. [47], who evaluated differences in HRQoL between these groups in tinnitus patients. These four independent symptom groups were defined as: (1) no symptoms of anxiety and depression, (2) symptoms of anxiety-only, (3) depression-only and (4) anxiety + depression.

Disease Severity

The UPDRS is a four-subscale combined instrument for assessing mental state, activities of daily living, motor examination and complications.

Two further instruments are used together with the UPDRS, namely: (1) a modified H&Y staging and (2) the Schwab and England Scale. It is currently used as a standard reference scale in clinical practice and research [19–21]. We used the UPDRS-III section for our research.

Data Analyses

Fisher's exact test and the difference between proportions test [48] were used to compare H&Y staging groups on demographic and clinical characteristics and are presented as numbers and percentages. Continuous variables were normally distributed in the current study (Shapiro-Wilk, $p > 0.05$) and were therefore compared with Student's t test and are presented as mean ± SD. Because we were interested in whether the implications of co-occurrence of anxiety and depression had a stronger impact on fatigue when compared with single or no occurrence of anxiety or depression, levels of fatigue in subjects with no symptoms of psychological distress were compared with levels of fatigue in patients classified as having only symptoms of anxiety, only symptoms of depression as well as symptoms of both anxiety and depression. A post hoc test (with Bonferroni correction for capitalisation on chance in multiple testing) was applied to all tests to adjust for multiple comparisons, with $p < 0.01$ ($p < 0.05/5$ items) indicating statistical significance.

Cohen's effect size (ES) for unrelated groups was used to estimate the magnitude of the difference between two groups (mean difference score/the pooled standard deviation). According to Cohen's thresholds, an ES of <0.20 indicates a trivial difference, an ES of ≥0.20 to <0.50 a small difference, an ES of ≥0.50 to <0.80 a moderate difference, and ES ≥0.80 a substantial difference [49].

Next, a path model was analysed to test the estimates of the magnitude of the effects of disease severity and depression on the five dimensions of fatigue and to estimate whether our data fit the hypothesised model using structural equation modelling (SEM). SEM allows the inclusion of unidirectional effects, but no reciprocal relationships can be tested. Therefore, SEM is more appropriate for our study than standard multiple regression technique as it allows for simultaneous assessment of the strength and direction of the interrelationships among multiple dependent (MFI domains) and independent variables (UPDRS and Depression). SEM does not prove causality, but it tests whether the dataset, with its inherent covariance structure, supports or rejects the postulated direct and indirect effects or relationships between variables and has been advocated as the best approach in mediating models [50, 51].

For determining the model fit, we used multiple criteria as suggested by Bentler and Bonett [52]. Using LISREL 8.7, we tested a recursive model (see fig. 1) in which pathways go directly from the background (exogenous) variable disease severity (UPDRS) to the five dimensions of fatigue (MFI), and a pathway through which symptoms of depression mediate the influence of disease severity (UPDRS) on the extent of self-reported fatigue (MFI-20). To allow for mutual comparisons between the path coefficients, a completely standardised solution was used. The analysis was done with SEM using the maximum likelihood method. The fit of the model was evaluated by means of (i) the comparative fit index (CFI), (ii) the normed fit index (NFI), (iii) the non-normed fit index (NNFI), (iv) the standardised root mean square residual (SRMR), (v) the root

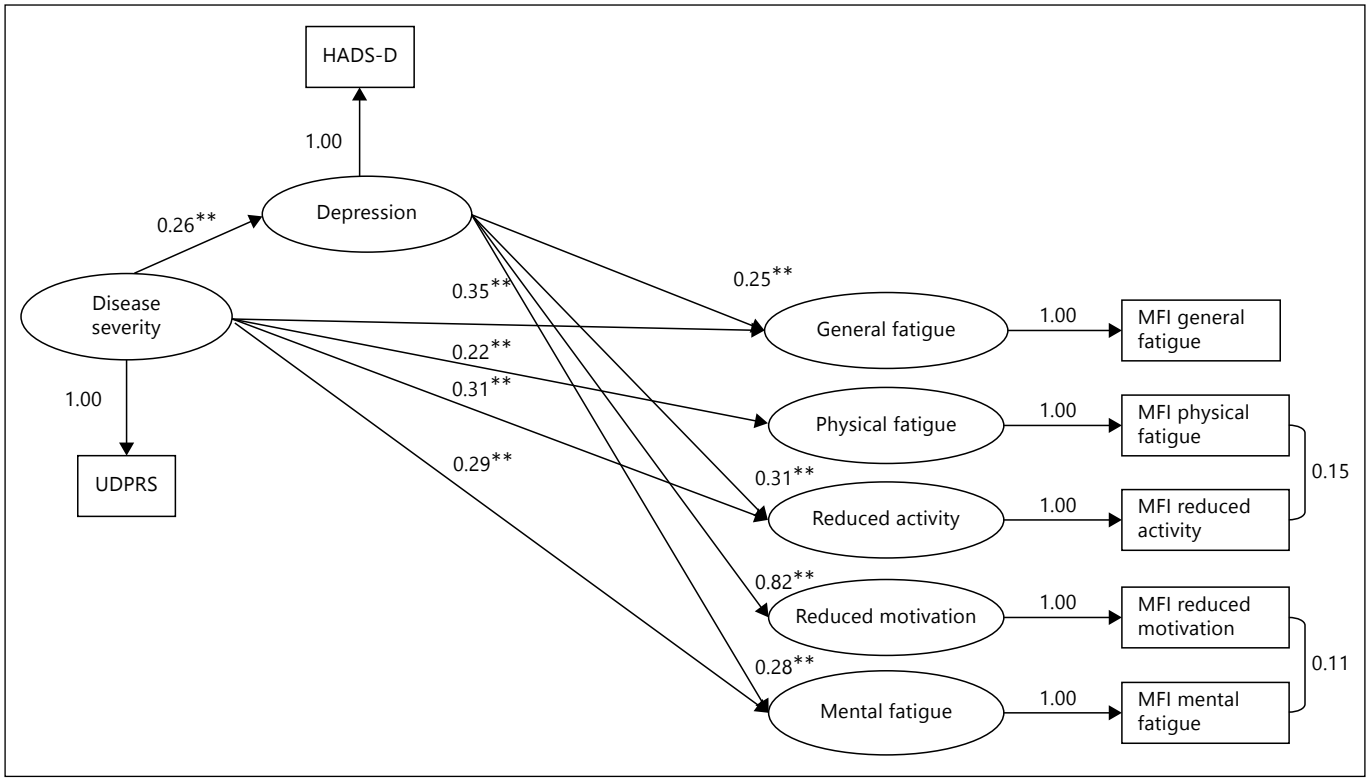

Fig. 1. A path model of disease severity and symptoms of depression as predictors of domains of fatigue assessed with the MF-20 in PD patients. Coefficients are all statistically significant: ** < 0.01. n = 190, $\chi^2 = 6.58$, d.f. = 5, p = 0.25, χ^2/d.f. = 1.06, NNFI = 0.98, CFI = 1.00, NFI = 0.99, SRMR = 0.020, RMSEA = 0.045.

mean square error of approximation (RMSEA) and (vi) the χ^2 test; a non-significant χ^2 indicates that a non-significant amount of variance in the data remains unexplained. An adequate fit of the model is indicated by NFI, NNFI and CFI ≥0.90, while SRMR <0.08, RMSEA <0.05 and NFI >0.90 are considered to indicate a good fit. The model was evaluated by examining the parameter estimates and measures of overall fit provided by LISREL. A residual correlation between depression and reduced motivation and between the domains of fatigue was allowed, since standardised residuals indicated that this correlation exists (not depicted). Only the path coefficients significant at the p < 0.05 level are depicted in the final model.

Results

Out of the 332 patients with PD who met the inclusion criteria, 126 did not respond to the invitation. Of the 206 who agreed to participate, 7 patients were eliminated because of the exclusion criteria and 9 patients refused to participate after written informed consent, thus leaving 190 for analysis (response rate 57.2%). Non-respondents did not differ significantly from the analysed group either in age (mean difference 1.6 years, 95% CI –0.80 to 4.0 years) or gender (Fisher's exact test, p = 0.08), with a difference between proportions of 9% (95% CI –3.0 to 12.4%). The mean age of the patients at baseline was 68.2 ± 9.3 years; the mean age at disease onset was 59.5 ± 11.1 years, and the mean disease duration was 6.4 ± 4.7 years.

Differences in Sociodemographic and Clinical Characteristics and Fatigue Measures across H&Y Subgroups

The use of dopamine agonists was more prevalent among patients classified as H&Y <2, whereas the simultaneous use of L-dopa + COMT inhibitors, L-dopa + dopamine agonists and L-dopa + COMT inhibitors + dopamine agonists was more prevalent among patients classified as H&Y ≥2. Other pharmaceutical treatment regimens were more prevalent among H&Y <2 patients.

Patients classified as H&Y ≥2 had on average longer disease duration (H&Y ≥2: 7.4 years vs. H&Y <2: 5.8 years) and had for all domains more symptoms of fatigue with clinically relevant differences with H&Y <2 (ES: 0.32–0.60).

Table 1. Sociodemographic and clinical characteristics of patients (n = 190) stratified by H&Y staging

	H&Y ≤2, N-115 n (%)	H&Y >2, N-75 n (%)	p value[1]	Difference between proportions, 95% CI
Male	58 (50.4%)	35 (46.7%)	0.15	–18.3 to 10.8
Female	57 (49.6%)	40 (53.3%)		
Antiparkinsonian therapy, n (%)				
L-Dopa	9 (7.83)	11 (14.67)	0.11	–16.2 to 2.55%
Dopamine agonists	31 (26.96)	5 (6.67)	0.40	10.4 to 30.2%
L-Dopa + COMT inhibitors	8 (6.96)	15 (20.0)	0.19	23.2 to 28.7%
L-Dopa + dopamine agonists	11 (9.56)	15 (20.0)	0.10	6.0 to 20.6%
L-Dopa + COMT inhibitors + dopamine agonists	9 (7.83)	14 (18.67)	0.14	7.1 to 20.9%
Other	47 (40.87)	15 (20)	0.31	8.1 to 33.6%
	mean ± SD	mean ± SD	p value[2] (ES)[3]	95% CI ES
Age, mean ± SD	67.5±8.6	69.7±10.3	0.178	
Disease duration	5.8±4.2	7.4±5.4	0.023 (0.34)	0.15 to 0.63
HADS-D	6.2±3.4	7.7±4.0	0.008 (0.42)	0.12 to 0.70
MFI – General fatigue	13.1±3.9	14.7±3.8	0.007 (0.41)	0.13 to 0.71
MFI – Physical fatigue	13.4±3.4	15.0±3.8	0.003 (0.45)	0.15 to 0.74
MFI – Reduced activity	11.7±3.4	13.8±3.8	0.000 (0.60)	0.29 to 0.88
MFI – Reduced motivation	10.4±3.4	11.6±4.4	0.049 (0.32)	0.12 to 0.61
MFI – Mental fatigue	11.2±3.5	12.8±4.0	0.007 (0.43)	0.14 to 0.72

[1] Fisher's exact test. [2] t test for independent samples. [3] ES for differences between groups.

Details of the sociodemographic and clinical characteristics of the patients stratified by H&Y staging are shown in table 1.

Differences in Domains of Fatigue across Psychological Distress Subgroups

Table 2 presents the results of bivariate evaluation of differences in domains of fatigue measures between the four psychological symptom groups. Levels of general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue were compared across the following independent subgroups: (1) anxiety-only, (2) depression-only and (3) anxiety + depression, which were compared with (4) patients without symptoms of psychological distress as a reference group.

Differences in levels of fatigue between no-symptoms and anxiety + depression subgroups (A–D) were large for all domains of fatigue (ES: 0.86–1.15), whereas differences in levels of fatigue were moderate between no-symptoms and depression-only (A–C), with ES ranging from 0.52 to 0.73 for the domains of general, physical and mental fatigue and reduced activity. Those patients who were classified as having only depressive symptoms showed a large difference compared with the group having no-symptoms. Moreover, upon comparing anxiety-only patients with patients having no symptoms of psychological distress (A, B), all differences proved to be due to random fluctuation ($p > 0.01$) after correction for multiple testing.

No differences in fatigue were found between those who reported no symptoms of psychological distress and those who reported only symptoms of anxiety. Therefore, we only used symptoms of depression in the model in relation to disease severity and fatigue. Figure 1 depicts the results of path analysis with LISREL 8.7, which shows the direct paths between disease severity (UPDRS) and depression (HADS) and the five domains of fatigue (MFI-20) as well as the mediated paths, which show the influence of disease severity on the domains of fatigue through higher numbers of symptoms of depression. Disease severity directly influenced symptoms of depression ($\beta = 0.26$) and directly affected fatigue in terms of more symptoms of general fatigue ($\beta = 0.35$), physical fatigue ($\beta = 0.22$), reduced activity ($\beta = 0.31$) and mental fatigue ($\beta = 0.29$), though it did not directly influence reduced motivation. However, more symptoms of depression mediated this impact of disease severity on more symptoms of

Table 2. Differences in domains of fatigue across psychological distress subgroups (n = 190)

	Group A No symptoms of anxiety or depression (n = 86)	Group B Symptoms of anxiety-only (n = 45)	Group C Symptoms of depression-only (n = 19)	Group D Symptoms of anxiety + depression (n = 33)	F	Effect size		
						A–D	A–C	A–B
General fatigue	12.04±3.89	13.74±3.43	14.68±3.57	16.33±3.22	12.40***	1.15***	0.70**	ns
Physical fatigue	12.63±3.67	13.01±3.24	15.00±2.36	15.94±3.44	8.96***	ns**	0.68**	ns**
Reduced activity	11.23±3.719	12.97±3.87	13.88±3.44	14.42±3.37	6.96***	0.88**	0.73**	ns
Reduced motivation	9.79±3.53	10.07±3.28	13.42±3.59	12.97±4.04	10.24***	0.86***	1.02**	ns
Mental fatigue	10.50±3.47	12.38±3.97	12.35±4.08	14.00±2.78	8.55***	1.06***	0.52**	ns

A post hoc Bonferroni correction was applied to all tests to adjust for multiple comparisons, with $p < 0.01$ (0.05/5) indicating statistical significance. Difference between groups with anxiety alone (A), depression alone (B) or no symptoms (C) were compared to the group with co-occurring symptoms of anxiety and depression (D) by means of ANOVA. F values are all significant at $p = 0.01$ level. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

general fatigue ($\beta = 0.25$), more symptoms of reduced activity ($\beta = 0.31$) and more symptoms of mental fatigue ($\beta = 0.28$). Reduced motivation was not mediated but directly influenced by more symptoms of depression ($\beta = 0.82$). More symptoms of physical fatigue in PD patients were not affected by higher levels of depression.

Discussion

The aim of our study was to test, using SEM, the hypothesis that the influence of disease severity on fatigue is mediated by symptoms of depression in patients with PD. We found (i) that disease severity is not a predictor of fatigue in terms of reduced motivation, but (ii) it is a precursor of more symptoms of general fatigue, physical fatigue, reduced activity and mental fatigue. Disease severity (iii) directly influenced symptoms of depression, and symptoms of depression (iv) mediated the impact of disease severity on higher levels of perceived general fatigue, more feelings of reduced activity and perceiving more mental fatigue. Symptoms of depression also (v) directly determined more symptoms of reduced motivation without the influence of disease severity. Finally, more physical fatigue in PD patients (vi) was not affected by more symptoms of depression. Symptoms of anxiety were not associated with MFI-20 domains of fatigue which was probably an effect of the fact that patients with enhanced fatigue are more at risk to develop symptoms of depression and less likely to develop symptoms of anxiety. This seems in contrast with previous results from this study.

Our results show that disease severity is a precursor of increased levels of general fatigue, physical fatigue, reduced activity and mental fatigue, but that disease severity is not related to fatigue in terms of reduced motivation. Furthermore, disease severity directly increased symptoms of depression. Mental fatigue and depression were generally considered to be independent of disease severity, whereas other studies have found an association between poor UPDRS and more symptoms of fatigue. In a longitudinal study, Alves et al. [53] found fatigue, measured by the generic Nottingham Health profile, to be related to disease severity. In a previous study, we found disease severity associated with worse fatigue in all fatigue domains as measured with the MFI [54]. In a recent study, Skorvanek et al. [28] found that none of the fatigue domains in primary fatigue (i.e. fatigue in the absence of a mood disorder or EDS) as measured by the MFI was associated with a worse UPDRS-III score. However, in the secondary fatigue group (i.e. fatigue in the presence of a mood disorder or EDS) they found that UPDRS-III scores were significantly related to all fatigue domains except mental fatigue. In the ELLDOPA trial [55], where untreated non-demented and non-depressed PD patients were examined, fatigue worsened significantly more in the placebo group than in the L-dopa groups, and some other studies have suggested a potential effect of dopaminergic treatment on at least some aspects of fatigue [56, 57]. However, fatigue in PD is generally considered to be a non-dopaminergic symptom. In fact, most studies have thus far not found any significant association between dopaminergic treatment or daily L-dopa equivalent dose and fatigue [24, 28, 53]. Similarly, we did not find an association between fatigue and

dopaminergic medication in our study (results not shown). The non-dopaminergic origin of fatigue in PD is also supported by the results of the previously mentioned ELLDOPA study [55], where fatigue scores did not correlate with the [^{123}I]-β-CIT SPECT striatal dopamine transporter density. Also, in a PET study conducted by Pavese et al. [58], an association between fatigue and a relative serotonergic denervation in the basal ganglia and associated limbic circuits and F-dopa uptake reduction in the insular region, but not in the basal ganglia, was found, thus suggesting a serotonin-related basis for fatigue in PD.

Several studies have shown a relationship between fatigue and depression and our previous study in 150 PD patients also had similar results [1]. Recently, Hagell and Brundin [3] found that depression is a main predictor of fatigue. Our results show that more symptoms of depression are associated with reduced motivation, and that symptoms of depression mediate the impact of worse functional status on mental fatigue, reduced activity and general fatigue. As was found in the study of Skorvanek et al. [28], PD patients with depression had both higher UPDRS-III scores and fatigue scores in all fatigue domains compared with primary fatigue; however, once depressed patients were selected, depression did not play a further role in determining fatigue in this group of patients. Their findings are in accordance with some other studies, which have found worse motor and fatigue symptoms in depressed patients [59]. From this point of view, secondary fatigue probably presents a more severe phenotype of PD with worse functional status, as well as more non-motor symptoms, such as depression and anxiety. On the other hand, more research is needed to reveal the underlying mechanisms of primary fatigue in the absence of depression.

Strengths and Limitations

One limitation of our study is the relatively low response rate. Patients were recruited mostly from outpatient neurologists, not from a specialised centre for PD care, and only those who agreed to participate were included. For this reason, only patients with better overall functional status came for the examination and interview. As a consequence, the current study comprised patients with lower UPDRS motor scores, while patients with severe disease were poorly represented in this study. However, we do not believe that this limits our observations. Although our results cannot be generalised to PD patients with all types of disease severity, we provide evidence that even in this selected population of PD patients, fatigue is already a serious problem. We decided to use a generic measure with a multidimensional design instead of a disease-specific fatigue measure, as this has the advantage of the possibility of using a generic instrument for different patient groups and consequently of comparing them. The association between depression and fatigue is still controversial because of the possible overlap in symptomatology between PD and major depression: fatigue and sleep problems are among the diagnostic criteria for both. However, to control for conceptual correlation between fatigue, depressive symptoms and parkinsonism, both factors were specified as an independent, one-directional contributor to fatigue and not as a recursive relationship in the path model used for this study. Moreover, a previous study using UPDRS and depression symptoms showed no multicollinearity as independent variables of fatigue assessed with the MFI-20 (variance inflation factor and tolerance values are 0.58 and 1.13, respectively).

Implications

Our study shows that disease severity predicts four domains of fatigue, but the presence of depression mediates this impact to three domains of fatigue and that disease severity and depression independently predict two of these domains. Evidence-based strategies on management of PD fatigue are scarce. Thus, in secondary fatigue an effort should be made to properly manage motor symptoms and depression, since at least some patients might benefit from these measures. Drug trials focused on depression in PD should include fatigue scales as secondary outcome measures, as only limited evidence in this regard is available, and some studies which have been conducted have thus far not found any significant improvement in fatigue symptoms after antidepressant treatment despite improvement of depression [60]. Further research, both cross-sectional and longitudinal, should be conducted in order to better understand the relationships between both primary and secondary fatigue and its influencing factors. Understanding this relationship is important, as it may influence the future clinical management of PD patients.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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